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November 20, 1998

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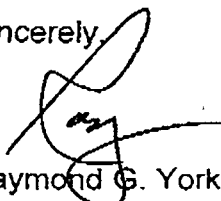
RE: Protocol 1613-002 - A Neurobehavioral Developmental Study of Ammonium
Perchlorate Administered Orally in Drinking Water to Rats
Sponsor's Study Number: 7757A210-1096-25F

Dear Ms. Jarabek:

Attached please find the missing page 3 from the Morphometric report you requested.

If you have any questions, please do not hesitate to contact me.

Sincerely,



Raymond G. York, Ph.D., DABT
Associate Director of Research
and Study Director

RGY:hmg
Enc.

ARGUS
PAGE 829Neuropathology Report
Morphometry Validation Study
Page 3 of 7**MORPHOMETRIC MEASUREMENT VALIDATION STUDY COMPARING
DAY 10 AND DAY 12 PUPS****SUMMARY**

Gross and microscopic morphometric measurements were performed on the brains of a total of 20 rat pups. The brains were from five male and five female rats that were 10 days of age and from five male and five female rats that were 12 days of age. The ages of 10 and 12 days were chosen to demonstrate that the measurement data from the selected neuroanatomic areas would reveal age-related developmental difference and might, therefore, be predictive of either an *in utero* neurotoxic effect or a delay in brain development. Two gross and seven microscopic measurements were taken.

The mean values for all of the neuroanatomic measurements were higher for the 12 day-old rat pups than for the 10 day-old pups, but there was considerable overlap between the Day 10 and Day 12 rat pup data, with the greatest measurement for at least one 10 day-old pup being greater than the lowest measurement for one of the 12 day-old pups. However, in spite of moderate data overlap between the two age groups and the presence of moderate intra-age group variability in the measurements for each neuroanatomic location, statistically significant increases (Day 12 versus Day 10 rat pups) were found for the following brain regions: anterior-posterior length of the cerebrum, anterior-posterior length of the cerebellum, thickness of the frontal cortex, width of the caudate-putamen, and height of the cerebellar cortex.

INTRODUCTION

The purpose of this study was to validate an approach to the performance of the morphometric component of those developmental neurotoxicity studies in which no microscopic neuropathologic lesions were encountered. A total of nine gross and microscopic morphometric measurements were taken. Rather than subjecting pregnant rats to a variety of neurotoxic agents, the decision was made to initially perform the morphometric measurements on rat pups of two different ages. The evaluated brains were, therefore, from male and female rat pups that were 10 and 12 days of age. Rat pups of these two ages were selected, because most developmental neurotoxicity studies include evaluations of brains from rat pups that are 12 days of age. Furthermore, our desire was to validate the hypothesis that differences in the measured neuroanatomic areas would be predictive of delayed development of the brain. The evaluated animals were all Sprague Dawley (CrI:CD®BR VAF/Plus®) rats.

MATERIALS AND METHODS**Study Overview and Group Assignments:**

The brains from a total of 20 Sprague Dawley (CrI:CD®BR VAF/Plus®) rat pups were evaluated. These brains were from five male and five female rats that were 10 days of age and from five male and five female rats that were 12 days of age.

Dissection and Trimming Procedures:

The brains had been immersion-fixed in 10% neutral buffered formalin (NBF) at the Testing Facility (Argus Research Laboratories, Inc.) and were received in NBF. These brains were intact and still within their cranial vaults. The calvaria covering the dorsum of each brain had already been removed to enhance fixation. The brains were removed and weighed. At the time of weighing, two linear measurements were taken from each brain using a Vernier caliper. These were: 1) a linear measurement of the cerebrum from the anterior to